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PROCEEDINGS OF THE TUMOR BOARD OF THE CHILDREN'S HOSPITAL OF PHILADELPHIA

Giulio J. D'Angio, MD, Series Editor, and Audrey E. Evans, MD, Associate Editor

Granulocytic Sarcoma

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Key words: chloroma, myeloblastoma, acute myeloid leukemia

Dhiren K. Shah, MD (Visiting Fellow in Radiation Oncology)

S.L. is an 18-month-old Chinese-American male who presented with a 2-month history of left peri-orbital swelling that was initially treated with antibiotics. There was no history of pain, fever, night sweats, change in activity or appetite, weight loss, bleeding, or bruising. Current medications include only Tylenol. Family history reveals his mother to have had a mastectomy for breast CA at age 32.

Physical examination revealed a healthy-appearing child. A swelling was apparent over the left cheek with peri-orbital edema. Pupils were equally round and reactive to light and his extraocular movements were intact. There were no cranial nerve deficits. There was no palpable adenopathy. Lungs were clear to auscultation bilaterally. Heart was regular in rate and rhythm. Abdomen was soft without any masses or hepatosplenomegaly. Neurologic exam was non-focal.

Hemogram was as follows: WBC 3.2 with ANC 1.4, Hgb 9.5, Hct 28.9, Plt 294K.

Jill Hunter, MD (Pediatric Radiologist)

MRI studies were helpful and revealed opacification of the sinus that is medium intensity on the T1 weighted images and slightly higher signal intensity on the T2 weighted images. Following gadolinium administration, there is a slight, diffuse enhancement of the lesion with a rim of more prominent enhancement (Fig. 1). The floor of the left orbit is bowed superiorly. There is a suggestion of cortical disruption, confirmed by CT scan (Fig. 2). The left eye is proptotic. Swelling is noted in the soft tissues superficial to the left maxillary bone (Fig. 3). The findings are suspicious for neoplasm. The differential diagnosis includes a soft tissue sarcoma, lymphoma, metastatic disease, or possibly mucocele.

Chest X-ray films showed no active disease.

Dr. Shah A bone marrow biopsy was negative for malignant cells. Dr. Uri will now present the histopathology.

Antonia Uri, MD (Pediatric Pathologist)

The biopsy slides show extensive infiltration of the orbital fat and muscle by large blasts and immature cells marked by some granularity of the cytoplasm (Fig. 3). The differential diagnosis based on the hematoxylin and eosin stain alone is difficult; however, we would favor chloroma rather than lymphoma because of the occasional cytosplasmic granularity. Special stains including also a panel of immunohistochemistry usually help to make the correct diagnosis. The naphthol-ASD-chloroacetate esterase stain (Leder stain) is specific for cytochemical identification of immature granulocytes, and is positive in the majority of the tumor cells here (Fig. 4). The lysozyme immunoperoxidase stain also is strongly positive, indicative of the granulocyte series. Other stains in the panel such as desmin for muscle origin and lymphocytic markers were negative. Therefore the diagnosis is granulocytic sarcoma or chloroma.

Dr. Shah It is interesting to recall that the error rate when only H&E stains were used was approximately 70%. These tumors before were called histiocytic lymphomas.

Charles Scher, MD (Pediatric Oncologist)

Were chromosomal analyses performed?

From the Departments of Radiation Oncology (D.K.S., J.G.), Pathology (A.U.), Radiology (J.V.H.), and Pediatrics (A.K., C.A.F.), The University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

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Fig. 1. Coronal T1-W post-gadolinium scan demonstrating diffuse, slight, enhancement with a rim of more intense enhancement from a left maxillary mass causing upward bowing and cortical disruption of the orbital floor. There is associated thickening of the left inferior rectus muscle.

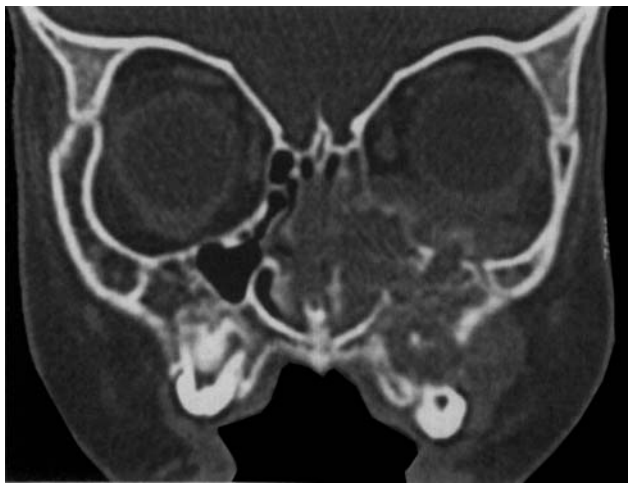

Fig. 2. Direct coronal, unenhanced CT scan performed four days after MRI. The bone window confirms destruction of the floor of the left orbit from a soft tissue mass apparently arising within the maxillary antrum and extending superiorly into the orbit, medially into the ethmoid air cells and inferolaterally down to the alveolar ridge, destroying the lateral wall of the maxilla.

Antonios Kattamis, MD (Pediatric Oncology/Hematology Fellow)

Chromosomal analysis was attempted but it was fruitless because the technique followed was that for solid tumors since, at the time of initial biopsy, this was considered to be a solid tumor. When the diagnosis became clear, treatment was started using the DCTER regimen, covered by granulocyte colony stimulating factor (GCSF). The DCTER regimen includes daunorubicin, cytarabine, thioguanine, etoposide, and dexamethasone.

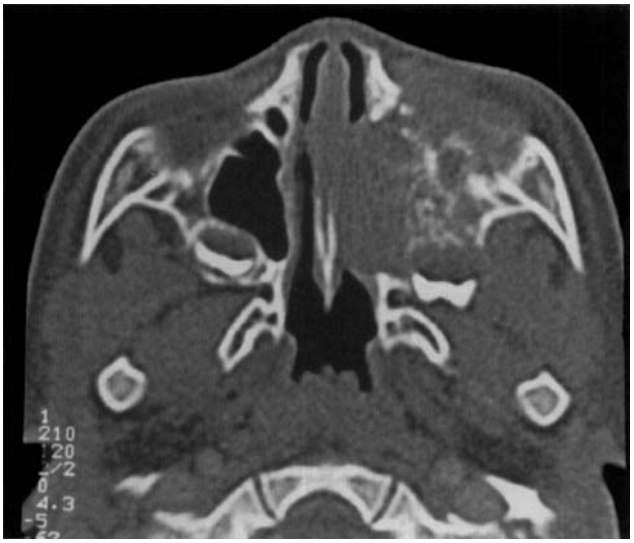

Fig. 3. Unenhanced axial CT performed at the same time as Figure 2 demonstrating loss of the anterior maxillary wall with associated thickening of the overlying soft tissues. There is bony spiculation, most likely due to residual normal bone. The soft tissue mass within the left maxillary antrum is again noted to destroy the alveolar ridge while extending into the left nasal cavity with loss of the medial wall of the maxilla. The right antrum appears clear.

Audrey Evans, MD (Pediatric Oncologist)

I suppose one point of discussion is whether systemic treatment should be given to a patient who has what seems to be a localized lesion.

Dr. Shah That question is difficult to answer on the basis of the available literature. Neiman et al. reported 13 of 15 patients in whom isolated granulocytic sarcoma progressed to acute myelogenous leukemia [1]. Based on this series, these patients are now typically treated as if they are newly diagnosed AML patients. The issue of radiation is also controversial. Chloromas are typically irradiated not because of any studies demonstrating improved local control or survival, but because of emergencies caused by chloromas impinging on vital structures. There are no studies that address the issue of irradiation on overall outcome, except to state that irradiation of isolated chloromas does not prevent the development of acute leukemia. In the Children's Cancer Group pilot study CCG-2861, all chloromas were not irradiated, and in two of the first 50 patients, the loci of unirradiated chloromas were the first sites of treatment failure.

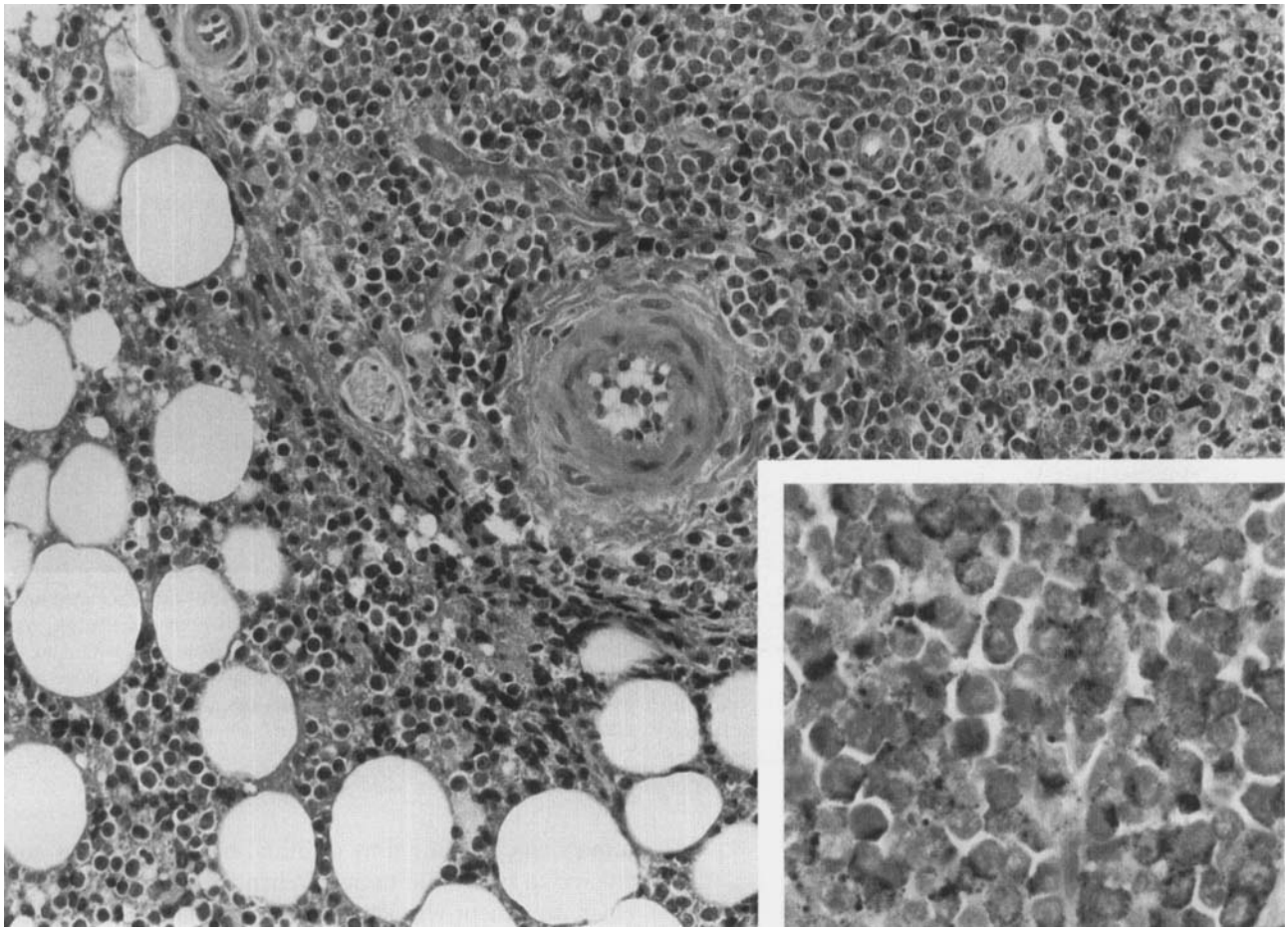

Fig. 4. Granulocytic sarcoma infiltrating adipose tissue and perivascular space in orbital region (hematoxylin-eosin stain, original magnification ×200) and showing positive cytochemical identification of myeloblasts. **Inset:** Naphthol-ASD-chloracetate esterase stain, original magnification ×400.

Jeffrey Silber, MD, PhD (Pediatric Oncologist)

Radiation therapy given to an 18-month-old is sure to produce some deformity. How deforming depends on the amount of residual growth of the irradiated part as well as age and dose factors.

Dr. Goldwein, how would you arrange your fields and what dose do you think would be appropriate?

Joel Goldwein, MD (Pediatric Radiation Oncologist)

The extensive involvement of the maxillary bone with tumor extending around the orbit makes the choice of fields and their arrangement extremely difficult. A "wedged pair," or an anterior and two lateral fields would be good arrangements, but blocks needed to protect the eye could easily "shadow" part of the tumor at the same time. In short, it would be a difficult and complex field arrangement. Compounding the difficulties would be the fact that sedation or anesthesia would be required to ensure immobility for the requisite precision.

Regarding dose, perhaps Dr. Shah can give us some guidance based on his review of the problem.

Dr. Shah Doses of 15–30 Gy have been used. These are similar to those employed in ocular leukemia where anthracyclines are not effective because it is a "sanctuary" site [2,3]. Granulocytic sarcoma has also been reported in the classic "sanctuary" site, i.e., the CNS and a similar dose was employed by Tornesello et al. [4]. As mentioned before, this patient has been placed on a protocol that requires all chloromas to be irradiated to 20 Gy in 10 fractions. All chloromas were not irradiated in the CCG pilot study with the results already described.

We reviewed 13 patients treated at the Hospital of the University of Pennsylvania aged 2.25 years to 16.24 years at diagnosis (median = 14.78). The doses they received were in the 10 Gy to 20 Gy range (median = 1457 cGy). There were four local failures. There is also a review of six patients under 20 years of age who presented with chloromas as a part of more generalized disease. It

appears in that patient group that irradiation did not impact on ultimate systemic relapse in those patients, but it may have decreased the risk of local relapse [5].

Dr. D'Angio, how much deformity would be produced by the 20 Gy this child is scheduled to receive?

Giulio J. D'Angio, MD (Pediatric Radiation Oncologist)

A general rule is that doses of 20 Gy or more are required in order to produce growth abnormalities. That general rule must be tempered by the point Dr. Silber makes so cogently; namely, deformity depends on the amount of residual growth in the irradiated region. There certainly are not many children in this age group who have had radiation to one side of the face to a level of 20 Gy. There may be some corollary evidence, however, from the long-term follow-up of children with acute lymphocytic leukemia who had cranial radiation at 18 Gy and 24 Gy. Dr. Silber, do these patients have grossly smaller head circumferences that can be appreciated visually?

Dr. Silber Absolutely. One can tell at a glance those children who had cranial radiation during early childhood.

Dr. D'Angio There is some parallel evidence from children irradiated for Wilms' tumor at 10 Gy. Dr. Evans went through the late effects of such treatment for the National Wilms' Tumor Study (NWTS); could you review those data for us, Dr. Evans?

Dr. Evans The NWTS has had an age-adjusted radiation dose since its inception in 1969; babies 1 year of age or under have always received about 10 Gy to the flank. Follow-up data have been requested through a mailed questionnaire. It is interesting that none of the babies given 10 Gy developed deformities sufficiently great that orthopedic intervention was required. This is not to say they had no deformity; it means that the growth suppression did not achieve proportions that required correction. How much can be adduced from that observation relative to a discussion of facial deformity is tenuous, but those are the facts derived from the NWTS files.

Dr. D'Angio Everyone's face is a little asymmetrical. The issue is whether 20 Gy would produce so much asymmetry that it would be considered disfiguring and therefore disabling. My estimate would be that 20 Gy would produce considerable conspicuous deformity in a child of this age, especially if a radiation enhancing agent such as an anthracycline—which this child is receiving—is added. Other body parts can be covered by clothing, but the face is exposed for constant inspection.

Dr. Goldwein How different is the outlook for a patient with chloroma versus a localized lymphoma?

Dr. Evans Lymphomas are associated with a better outlook, but granulocytic leukemia given sufficiently heavy chemotherapy is now more curable than at the time some of the data presented were gathered. Is radiation therapy really necessary in this child?

Dr. Scher The no-radiation treatment option is certainly worthy of consideration. A 4% relapse rate in the nonirradiated CCSG sample is really not bad.

Dr. Shah That is true, and in any case there is no clear evidence that giving local radiation therapy prevents the evolution of the disease to a frank acute myeloid leukemia (AML).

Dr. D'Angio Dr. Kelly, you have spent some time at the Hospital for Sick Children, Great Ormond Street, our sister institution in London; could you tell us what you think your English colleagues might decide to do in a case like this?

Kara Kelly, MD (Pediatric Oncology/Hematology Fellow)

I cannot presume to say what the team there might do in this particular instance. The few chloromas I saw during my year in London were not irradiated, and my impression is that patients with chloromas given chemotherapy have a better outlook than those who have frank AML.

Dr. D'Angio The consensus appears to be not to irradiate this child given all the problems that have been discussed until or unless there is a residual mass visible on imaging studies after an appropriate trial of chemotherapy.

On a quite different matter, it is noteworthy that the mother has had breast cancer at the age of 32. It raises the possibility that this child is a member of a Li-Fraumeni family.

ADDENDUM

Carolyn A. Felix, MD (Pediatric Oncologist)

The child and mother were studied for evidence of a p53 gene mutation. Germline p53 mutations may confer a phenotype that facilitates the early development of breast cancer and acute myeloid leukemia, both constituent tumors of the Li-Fraumeni syndrome, and both present in this family [6,7]. The p53 tumor suppressor gene also was a candidate gene to examine in orbital oculogranulocytic sarcoma (OOGS) because chromosome 17p abnormalities and p53 mutations are present in some cases of de novo AML. In earlier studies of de novo AML, consistent elevations of p53 protein have suggested a role of abnormal p53 [8]. p53 gene mutations have been observed in AML, especially in association with cytogenetic evidence of 17p monosomy [9]. In one model of the role of altered p53 in oncogenesis, wild-type p53-mediates a growth-inhibitory G1 arrest, the essential period in the cell cycle for either DNA repair before replication or for apoptosis, and p53 gene mutations result in loss of the capacity for DNA repair [10]. It is possible that the pathogenesis of AML occasionally may involve a genetic pre-

Fig. 5. Unenhanced axial CT performed 8 months after the initial scan, showing reconstitution of the anterior and medial walls of the maxilla and left-sided alveolar margin. The left naris is clear but there is a little soft tissue thickening within the right maxillary antrum, most likely due to sinus disease.

disposition. The Li-Fraumeni syndrome of multiple primary cancers in individuals or in families includes AML but germline p53 gene mutations have not yet been identified in AML in the Li-Fraumeni syndrome, or in familial leukemia pedigrees [11]. p53 mutations also are present in approximately 22% of cases of sporadic breast cancer [12]. A small proportion of women with early onset breast cancer have germline p53 mutations [13,14].

Screening for p53 mutations Genomic DNAs were prepared from the diagnostic marrow of the child that was negative for leukemia, and from peripheral blood of the affected mother. Using oligonucleotide primers that have been reported, these specimens were screened by the PCR/SSCP method for constitutional mutations in the p53 gene [15–17]. PCR fragments containing exons 5 and 6, or exons 7 and 8 incorporating [^{32}P]-dCTP were amplified using 100 ng genomic DNA as a template. Aliquots of the PCR products then were digested with the restriction enzymes *Aat*I or *Dra*I, respectively, to reduce the sizes of fragments to those suitable for SSCP and to localize any pattern differences. Reactions were diluted with loading buffer, denatured by heating to separate the single strands, and electrophoresed in non-denaturing acrylamide using the same conditions as described [15]. Although mutations in other regions of the p53 gene were not excluded, these studies did not suggest a constitutional mutation of the gene in the regions most commonly affected in the cancers of the Li-Fraumeni syndrome.

Dr. Kattamis The child is well and free of disease for 9 months, and Dr. Hunter reports excellent remineralization of the facial bones (Fig. 5). He is currently on the last phase of chemotherapy that includes four cycles of DCTER and two cycles of cytarabine and asparaginase followed by three cycles of thioguanine, vincristine, cytarabine, 5-azacytidine, cyclophosphamide, amd one cycle of etoposide, daunomycin, cytarabine, and dexamethasone.

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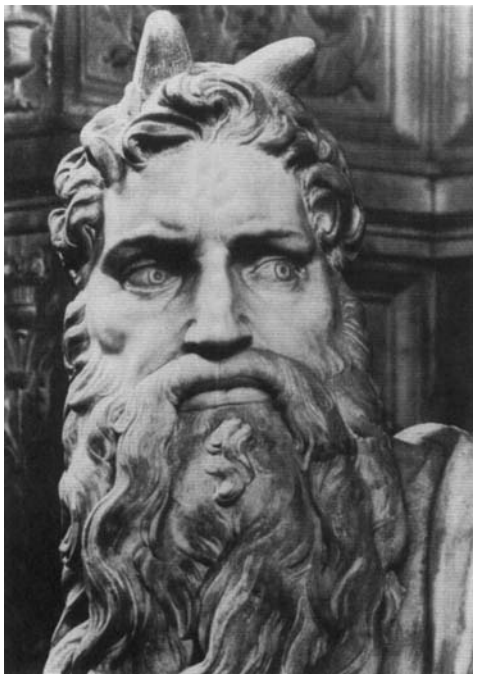

Fig. 6. Moses, the "horned" patriarch, by Michelangelo.

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Series Editor's Note

Many medical terms stem from homely comparisons, e.g., *chloroma* because of its green color. Others have more exotic (Greek: "from another country") origins, and many from theological (Greek *the* (god) + *logia*(to speak of) allusions, most often to mythologic figures and tales. The *delphic node, caput medusae, cyclopedia, narcissisn,* and the *electra* and *oedepus* complexes are some in common use.

Later religions have made their contributions, of course, and a mistranslation produced a medical curiousity of sorts. The Hebrew verb *qāran* used in Exodus 34:30, stems from the noun *qéren*, meaning "horn." In context, *qāran* has the meaning "sending out rays," and thus describes Moses' lumious visage on his descent from Mt. Sinai. St. Jerome, however, remembering *qéren,* erred in rendering *qāran* as *cornuta* (horned) in his monumental Latin translation of the entire Bible, the so-called Vulgate. The mistake thus yielded not a "radiant" Moses as intended but a "horned" patriarch, the oddity so depicted in the famous statue by Michelangelo in S. Pietro in Vincoli (St. Peter in Chains) in Rome (Fig. 6.)[1]

As a parenthesis here, S. Levin has provided an interesting speculation for the disturbance in Moses' speech, usually attributed to stuttering. Dr. Levin makes a case for Moses actually having had a hare lip and/or cleft palate (J Royal Soc Med 85:632–633, 1994).

Hurried recital of the Lord's prayer in Latin (*Pater Noster*) gave rise to *patter* (= rapid speech) in English. *Brouhaha* (noisy, excited upset, uproar) seems onomatopoetic,[2] but apparently via devious paths stem from the Hebrew religious phrase, *Barukh Habba,* meaning "Blessed be he who enters." This phrase in perverted form was used in an ancient French farce at a tumultuous moment in the plot. Another word with similar connotations is *Bedlam,* a place or condition marked by constant tumult. It is a corruption of *Bethlehem,* the Saint Mary of Bethlehem Royal Hospital in London having been founded to house the mentally ill.

To return to more medical terms, *St. Anthony's fire* (ergotism; erysipelas) and *St. Vitus' dance* (choreaform motions associated with rheumatic fever) were until recently heard often in medical parlance. Also with a medical basis, albeit through a tortuous route, is *tawdry.* Etheldreda, 7th century queen of Northumbria, renounced her throne and became a saintly nun, her name having become simplified to "Audrey." She eventually died of a throat ailment. An ornamental lace collar worn in her memory was termed "St. Audrey's lace," in time shortened to *tawdry lace.* It was sold at fairs at low prices and became synonymous with showy but shoddy[3] merchandise; hence *tawdry.* There is today a St. Etheldreda's church in Ely Place, London, recalling the saint and the monastery (the Greek root meaning "to live alone") on the Isle of Ely (which is not actually an island but a marshy expanse) of which she became the abbess. *Ely* derives from "eels" which were abundant in the region and perhaps still are.

[1]The help of Prof. R.W. Corney of the General Theological Seminary, New York City, NY; Dr. Sahar Rosenbaum of Camden, NJ; and in Rome, Italy, Dr. and Mrs. S. Fasanelli, and Drs. G. and A. Iannaccone is gratefully acknowledged in the un-horning of Moses.

[2]See Med Pediatr Oncol 18:327–328, 1990.

[3]A type of mediocre wool made to look better than it is, the word now used mainly to denote inferior quality.